UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,935	01/24/2005	Bruno Stuhlmuller	BB-126	2083

23557 7590 02/21/2008
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
02/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,935	STUHLMULLER ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *19-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-9 and 32 in the reply filed on 12/3/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly claims 19-31 has been withdrawn from consideration as being drawn to a non-elected invention. The claims 10-18 have been canceled.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-9 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are broadly drawn to an array comprising any oligo- or polynucleotide probes of the selective monocyte macrophage genes in Table 1 to 6, any further gene known to be expressed in a cell and to constitute part of the basis genotype cells, any gene or partial or oligomer sequence that are selected genes of rheumatoid arthritis or other chronic inflammatory diseases, any alleles, derivatives and/or splicing variants of the gene or partial gene sequence

and oligomer sequences, and any gene which present a partial sequence identity of at least 80% in the protein coding mRNA segment and homologs from other species and other genes and sequences as well. The claims encompass a plethora of nucleic acid species not adequately described or disclosed. In support of the broad genus recited above, the specification only provides a list of genes by an Affymetrix internal designation number and an accession number with the name of the gene. No sequence structures, alleles, variants, sequences having at least 80% identity to the genes of Tables 1-6 or homologs of the genes recited the Tables are provided. Applicant does not provide any support for an array structure comprising a cluster of the undisclosed nucleic acid species.

A representative number of nucleic acid species for each genus must be disclosed to meet the written description requirement of 112, first paragraph. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species, because there may be unpredictability in the

results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented invention of any species other than the one disclosed." *In re Curtis*, 354 F3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)". With respect to each recited gene as recited in the claim 32, neither the specification nor claims provides any guidance as to whether the sequences applied to array are to be limited to sequences comprising the sequences of the accessions listed in the description of the sequences.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whaterever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is separable from the enablement provision. *In the Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence falling within the scope of the claimed genus. At section B(1), the court sates that 'An adequate written description of a DNA....'requires a

precise definition such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the claims recites an Affymetrix internal designation which is indicative of a Genbank accession number, which do not provide for a fixed sequence as sequences in Genbank can change, while retaining the same accession number. Accordingly, the recitation of Genbank Accession number does not provide for a specific sequence. For example, for the calcium channel alpha 2 delta subunit which is represented with the Affymetrix internal designation 219714_s_at, the Genbank accession number NM_018398.1 as recited in the specification at Table 1 has had 1 revision to the sequence. For the U6 snRNA-associated Sm-like protein (LSM4) which is represented with the Affymetrix internal designation 202737_s_at, the Genbank accession number NM_012321.1 as recited in the specification at Table 1 has had one revision to the sequence. However, neither the specification nor the claims provide any guidance as to which sequence is to be part of the claim array. Further although an actual nucleotide sequence is viewable in Genbank, the claims encompass the full gene sequence, which are not provided by the sequence that corresponds to the recited Accession number listed in the Table 1. The specification provides no guidance on how to make derivative sequences (mutants, alleles, variants, splice variants, etc.) of the gene sequences that would retain its ability to hybridize with their intended target polynucleotide and be used in array hybridization assays to screen for specific

diseases, such as rheumatoid arthritis or other chronic inflammatory diseases. The specification provides no guidance as to the nucleic acid substitutions, deletions, or insertions that can be present in a given gene sequence that are broadly encompassed by the claims.

As set forth by the Court in *Vas Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date Applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of the species as claimed in claims 1-9 and 32 of the specification fails to show that Applicant was, in fact "in possession of the claimed invention" at the time the application for patent was filed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-9 are indefinite at the recitation of "characterized in that" it cannot be determined how the claimed scope is affected. It is suggested that typical US claim language be used.

(b) The claim 4 is indefinite and confusing at "the genes, their partial and oligomer sequence... of rheumatoid arthritis or other chronic inflammatory diseases" because it is not clear what genes Applicant is making reference to. Further, it is not clear the nexus between the claimed genes recited in the claim 4 and the probes recited in the claim 1. Additionally, it cannot be determine if Applicant is making reference to a separate and distinct element of the array.

(c) The claim 5 is indefinite and confusing at "the genes, their partial and oligomer sequences... of the monocyte/macrophage cell system" because it is not clear what genes Applicant is making reference to. Further it is not clear the nexus between the claimed genes recited in the claim 5 and the probes recited in the claim 1. Additionally, it cannot be determine if Applicant is making reference to a separate and distinct element of the array.

(d) The claim 6 is indefinite and confusing because it is unclear at to what alleles, derivatives and/or splicing variants or partial gene sequences applicant is making reference to. Neither the claims nor specification recited any specific alleles, derivatives and/or splicing variants or partial gene sequences. Thus a clear interpretation as to what is to be present on the array cannot be ascertained.

(e) The claim 7 is confusing for the recitation of gene sequences which present a partial sequence identity of at least 80% in the protein coding mRNA segment. Normally, this recitation is taken to be a comparison between two sequences to score the identity between the nucleotides (or amino acids) between the two sequences. However, no specific sequences are set forth in the claim 1 from which the claim

depend for the artisan to ascertain if a sequence ha "80% sequence identity" top the molecule(s) in claim 1. The specification provides no added definition to determine the requisite degree needed to meet the limitations of the claim. Accordingly, the metes and bound are unclear. Further it is not clear if the 80% identity is further defining the genes in claim 1 or if it is in reference to additional sequences other than those recited in the claim 1.

Claim interpretation

6. The claims 1-9 and 32 as currently written are extremely broad and ambiguous. Likewise, the specification does not provide a clear description or definition of the terms recited in the claims. Accordingly, clear interpretation of Applicant's intent cannot be ascertained. Therefore, for the purpose of application of prior art, such recitations of genes, partial genes, oligomer sequences, sequence having 80% identity, alleles, derivatives and variants are being interpreted by the Examiner to be any sequences that are selected to be associated with a solid support

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-9 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern et al (5981956, November 1999). Regarding claims 1-9 and 32, Stern et al

teaches an array of oligonucleotides containing all possible combination of oligomers that would contain sequences of all the genes listed in the Tables 1 and 2 of the instant specification (see col. 6, lines 10-18 and claims). Stern teaches that the array can be composed of glass or silica and can have surface Si-OH functionalities (col. 5, lines 29-30, 39-47). Stern further teaches that polymers can be immobilized on the above described arrays using light directed synthesis methods (col. 5, lines 48-67). Stern teaches that the probe array may be designed to specifically to detect genetic diseases, either from acquired or inherited mutations in an individual (col. 7, lines 15-18). Accordingly, Stern et al meet the limitations of the claims as broadly written.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-9 and 32 are rejected under 35 U.S.C. 102(a) and/or 35 U. S.C. 102(e) as being anticipated by Orntoft (US 6335170, publication date January 1, 2002, effective filing date February 1999). Regarding claims 1-9 and 32, Orntoft teaches an Affymetrix probe array comprising oligonucleotide probes comprising a selection of

sequences corresponding to the genes recited in the Tables 1 and 2 (see Example 1, col. 9-10; see also Example 5 and Tables 1-9 which recites a list of genes such as those recited in the Tables 1 and 2 of the instant invention, e.g., 211654_x_at). Orntoft teaches that the arrays are high density expression arrays (col. 7, line 17). Thus Orntoft meets the limitations of the claims as broadly written.

11. Claims 1-9 and 32 are rejected under 35 USC 102(e) as being anticipated by Pittman et al (US 20030154032, December 2000). Regarding claim 1-9, Pittman et al teach synthesis of an Affrymetrix microarray comprising 400,000 oligonucleotides comprising a selection of sequences corresponding to the genes recited in the Tables 1 and 2 (0126 and 0127, Tables 1-5 which recites a list of genes such as those recited in the Tables 1 and 2 of the instant invention, e.g., FCGRT). Pittman teaches that the array may comprise glass or metal (0134). Pittman teaches that the arrays of oligonucleotides may be synthesized by light-directed combinatorial synthesis (0136 and 0139). Pittman teaches that the probes may correspond to the full length RNA or complement thereof of genes characteristic of rheumatoid arthritis or portions there of (00123) Pittman teaches that the nucleic acid probes on the array may be natural, chemically modified (00140). Thus, Pittman meets the limitation of the claims as broadly written.

12. Claims 1-9 and 32 are rejected under 35 USC 102(a) as being anticipated by Fodor et al (US 20010053519, December 2001). Regarding claims 1-9 and 32, Fodor

et al teach arrays of oligonucleotides containing all possible combinations of 2-mer, 10, and 25-mer sequences that would contain sequences of all the genes listed in Table 1 and 2 of the instant invention (see paragraphs 0075-0077 and 0101). Fordo teaches that the array can be made of agarose that is activated by CNBr so that polynucleotides can be covalently attached (paragraph 0075). Fodor teaches that the oligonucleotides can be synthesized and immobilized on the above array using light directed synthesis methods (see 0063). Fodor teaches that RNA polynucleotides can be attached to the array (paragraph 0101 and 0016). Therefore, Fodor meets all of the limitations of the claims as broadly written.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-9 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stuhlmuller et al (citation made of record on IDS filed 7/20/2006) in view of Heller et al (citation made of record on IDS filed 7/20/2006). Regarding claims 1-9 and 32, Stuhlmuller et al teaches novel genes in monocytes from patients detected via differential hybridization techniques using probes isolated cDNA library constructed from leukapheresis monocytes (see entire reference, especially, pages 777-778; tables 1-5 and Figures 1-3).

Stuhlmuller et al does not expressly teach wherein the oligonucleotide probes are immobilized on a solid substrate such as array.

Heller et al teaches cDNA microarray for analysis of inflammatory disease-related genes. Heller et al teaches wherein cDNA sequences or cDNA inserts of a library are arrayed on a glass slide with high speed robotics at a high density of 1000 cDNA per cm^2. Heller teaches that the microarrays server as gene targets for hybridization to cDNA probes prepared from RNA samples of cells or tissues (col. 1, page 2150). Heller teaches that a microarray is advantageous because of the speed, ease and feasibility of simultaneously monitoring differential expression of hundreds of genes that may be associated with a complex disease such as rheumatiod arthritis (page 2154, col. 2 under "Discussion").

One of ordinary skill in the art at the time of the claimed invention would have been motivated to apply the cDNA oligonucleotides constructed from leukapheresis

monocytes as taught by Stuhlmuller et al onto a microarray for the obvious benefits of speed, ease and feasibility of simultaneously monitoring differiential expression of hundreds of genes associated with complex diseases, such as RA as taught by Heller et al.

Conclusion

17. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Patent Examiner
Art Unit 1637

2/6/2008